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D E C I S I O N
of 23 March 2004

Case Number: T 0735/00 - 3.3.4

Application Number: 90906370.3

Publication Number: 0431171

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:
Monoclonal antibody against c-reactive protein

Patentee:
IATRON LABORATORIES, INC.

Opponent:
Dade Behring Marburg GmbH

Headword:
Anti-CRP antibodies/IATRON LABORATORIES, INC.

Relevant legal provisions:
EPC Art. 114(2), 83, 123(2)(3), 54, 56

Keyword:
"Late filed auxiliary requests 1 to 3 - admissibility - (yes)"
"Novelty - main request and auxiliary request 1 - (no)"
"Inventive step - auxiliary requests 2 and 3 - (no)"

Decisions cited:
T 0512/94, T 0645/02

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0735/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 23 March 2004

Appellant I: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 24 May 2000 concerning maintenance of European patent No. 0431171 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: A. L. L. Marie
R. A. M. Moufang

Summary of Facts and Submissions

I. European patent EP 0 431 171 with the title "Monoclonal Antibody against C-reactive Protein" was granted on the basis of a set of seven claims, claims 1 to 3 of which read:

"1. A monoclonal antibody specifically reacting with the side face of a disk-like subunit of a C-reactive protein."

"2. A monoclonal antibody capable of carrying an agglutination reaction due to an antigen-antibody reaction with the side face of a disk-like subunit of a C-reactive protein, when immobilized on an insoluble carrier."

"3. A monoclonal antibody selected from the group consisting of monoclonal antibody CRP-1 obtainable from hybridoma cell line CRP-1 (FERM BP-2873), monoclonal antibody CRP-2 obtainable from hybridoma cell line CRP-2 (FERM BP-2874), monoclonal antibody CRP-3 obtainable from hybridoma cell line CRP-3 (FERM BP-2875), and monoclonal antibody CRP-4 obtainable from hybridoma cell line CRP-4 (FERM BP-2876)."

II. Notice of opposition was filed and the revocation of the patent in suit was requested on the grounds of Article 100(a) EPC, for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and of Article 100(b) EPC for insufficiency of the disclosure (Article 83 EPC).

III. The opposition division maintained the patent in suit pursuant to Article 102(3) EPC on the basis of the single claim of an auxiliary request before them which read:

"1. Use of a single monoclonal antibody selected from the group consisting of monoclonal antibody CRP-1 otainable from hybridoma cell line CRP 1 (FERM BP-2873), monoclonal antibody CRP-2 obtainable from hybridoma cell line CRP-2 (FERM BP-2874), monoclonal antibody CRP-3 obtainable from hybridoma cell line CRP-3 (FERM BP-2875), and monoclonal antibody CRP-4 obtainable from hybridoma cell line CRP-4 (FERM BP-2876) and capable of carrying an agglutination reaction due to an antigen-antibody reaction with the side face of a disk-like subunit of a C-reactive protein, when immobilized on an insoluble carrier in a latex agglutination immunoassay."

IV. Appeals against the decision of the opposition division were filed by appellant I (the patentee) and appellant II (the opponent).

V. The Board issued a communication pursuant to Article 11(1) of the rules of procedure of the Boards of Appeal giving the Board's preliminary and non-binding opinion on the evidence filed by the parties in view of the existence of a C- or side face in the C-reactive Protein molecule (CRP), the conclusions drawn from experimental reports, the experimental conditions used and the proposal to have the experimental reports submitted by both appellants be reproduced by an independent expert.

VI. Oral proceedings were held on 23 March 2004, during which appellant I filed auxiliary requests 1 to 3. Claim 1 of auxiliary request 1 read:

"1. A monoclonal antibody capable of performing an agglutination reaction due to an antigen-antibody reaction with the side face of a disk-like subunit of a C-reactive protein when immobilized on an insoluble carrier."

Claim 1 of auxiliary request 2 read:

"1. A monoclonal antibody selected from the group consisting of monoclonal antibody CRP-1 obtained from hybridoma cell line CRP-1 (FERM BP-2873), monoclonal antibody CRP-2 obtained from hybridoma cell line CRP-2 (FERM BP-2874), monoclonal antibody CRP-3 obtained from hybridoma cell line CRP-3 (FERM BP-2875), and monoclonal antibody CRP-4 obtained from hybridoma cell line CRP-4 (FERM BP-2876)."

Auxiliary request 3 had a single claim which was the one the subject-matter of which was held by the opposition division to fulfil all requirements of the EPC (see section III above) with the sole amendment of a comma before the expression "...*in a latex agglutination immunoassay*."

VII. The following documents will be referred to in the present decision:

(1) K.H. Roux et al., Journal of Immunology, 1983, Vol. 131, No. 5, pages 2411 to 2415

(2/2*) Abstract (Derwent, AC 87-274903/39): JP 62-192661-A

(3/3*) Abstract (Derwent, AC 87-040957/06): JP 62-000498-A

(4) H. Hirai et al, Protides of the Biological Fluids, Proceedings of the 3th Colloquium, 1986, pages 283 to 286

(5) EP-0 246 446

(6) Declaration under Rule 132 before the USPTO of Dr. G. Soe, dated 13 August 1992 in re the application of Gilbu Soe et al. Serial No 635,616

(7) Figure submitted by patent proprietor (appellant I) with letter of 30 October 1996

(8) Memorandum "Untersuchungen zur Agglutination von monoklonalen Antikörpern gegen CRP" submitted by opponent (appellant II) with letter of 3 March 1998

(10) Memorandum "Untersuchungen zur Agglutination von monoklonalen Antikörpern gegen CRP" dated 17 December 1998 submitted by opponent (appellant II)

(11) Erklärung an Eides Statt of Dr. H. Harthus dated 8 September 1999

(12) Memorandum "Untersuchungen zur Agglutination von monoklonalen Antikörpern gegen CRP" dated 8 September 1999 submitted by opponent (appellant II)

(17) Modified Figure of document (7)

(24) Experimental Report of Professor T. Okuyama dated 30 August 2000, submitted by patent proprietor (appellant I) with letter of 29 September 2000

(25) Memorandum "Untersuchungen zur Agglutination von monoklonalen Antikörpern gegen CRP" dated 27 March 2001 submitted by opponent (appellant II)

(27) Document filed by appellant I to illustrate Experiment 3-2 of document (24)

Documents 2* and 3* are the English translations of the Japanese patents corresponding to the cited abstracts.

VIII. The arguments submitted by appellant I as far as they are relevant for this decision may be summarised as follows:

Article 114(2) EPC

Auxiliary requests 1 to 3 filed during the oral proceedings could not have taken appellant II by surprise, since the claims of auxiliary request 3 only differed from those of the auxiliary request having been the basis of the decision of the opposition

division by the addition of a comma and the claims of auxiliary requests 1 and 2 were restricted to subject-matter already defined in some of the independent claims as granted.

Article 123(2)(3) EPC
Auxiliary request 1

The objections raised under this provision of the EPC by appellant II were answered.

Article 54 EPC
Main request

Evidence of the existence of the CRP C- or side face was provided in Figure 1 of the patent in suit, in the electron microscopy and computer pictures of document (24) and in the disclosure of document (1), in which the Fab monoclonal antibody molecules were said on page 2412 to protrude at nearly right angle from the *planar surfaces* of CRP and the CRP subunits depicted as spheres only *for simplicity*.

The small size of the CRP molecule rendered improbable the existence of other epitopes on the A-and/or B-face on which the antibodies CRP-1 to CRP-4 could bind. This was also deduced from document (7), a schematic representation at scale of latex particles, CRP and antibodies, which made clear that steric hindrance would prevent agglutination by reaction of CRP with antibodies binding on a face other than the C-face and from *Experiment 3-2* of document (24).

Furthermore, as far as the reproducibility of the teaching of the patent in suit was concerned, it was indicated in Example 4 of the patent in suit that the A- and B-face antibodies used were disclosed in the prior art document (1) and that the feature allowing the identification of a C-face specific antibody was its ability to agglutinate CRP when immobilized on latex particles.

Article 54 EPC
Auxiliary request 1

The monoclonal antibodies described in the patent in suit bound to the side or C-face of a disk-like subunit of CRP and, when immobilized on an insoluble carrier, led to an agglutination reaction with CRP due to an antigen-antibody reaction. On the contrary, the monoclonal antibodies of the prior art documents (1) to (4) neither bound to the C-face nor led to an agglutination reaction with CRP, as shown in the patent in suit (page 7, lines 15 to 17) and in documents (6), (7), (24) and (27), and were hence different from those described in the patent in suit. These results were in contradiction with those provided by the experimental reports of appellant II (documents (8), (10), (11), (12), (17) and (25)), whose proposal to have them reproduced by an independent expert was agreed to.

Article 56 EPC
Auxiliary requests 2 and 3

If any one of documents (2) and (5) was considered as the closest prior art, the problem to be solved was to improve the sensitivity of the CRP determination assay

disclosed therein and the solution offered in the claims of these requests could not be deduced in an obvious manner from the prior art, since nothing therein suggested the use of agglutinating anti-CRP antibodies whose ability to agglutinate CRP represented an unexpected effect.

IX. The arguments put forward by appellant II as far as they are relevant for this decision can be summarized as follows:

Article 114(2) EPC

The filing of auxiliary requests 1 to 3 during the oral proceedings was not justified, since the last submission of appellant II was filed in April 2001 and since the Board had set up in its communication a time limit of two months before the oral proceedings for further submissions.

Article 123(2)(3) EPC
Auxiliary request 1

The term "*performing*" mentioned in claim 1, 3 and 5 of auxiliary request 1 had a meaning different from the term "*carrying*" as used in claim 2 as granted and in the application as filed and amounted to a violation of the requirement of the above article.

Article 54 EPC
Main request

CRP C- or side-face was described in terms of structure neither in the prior art, nor in the patent in suit.

The electron microscopy pictures of documents (1) and (24) were not of a sufficient quality for assessing the existence of CRP C-face. No indication was given in document (24) on how the electron microscopy picture lead to the computer model. The schematic diagram of document (7) was no evidence of the existence of the CRP C-face, as shown in document (17).

In the patent in suit A- and B-face specific antibodies were used, the preparation of which was not sufficiently disclosed and the screening used therein was not reproducible. There being no disclosure of the C-face, this cannot be regarded as a technical feature and thus either the alleged invention was not enabled or not novel, the latter because no clear boundary could be drawn to those monoclonal antibodies which were already described in prior art documents (1) or (2) to (4) to bind on CRP.

Auxiliary request 1

The antibodies disclosed in documents (2) to (4) were shown in documents (8), (10), (11), (12) and (25) to precipitate - and thus to agglutinate - CRP and to inhibit the binding of the antibodies CRP-1 to CRP-4 of the patent in suit onto CRP. In documents (8) and (12) this teaching was extended to antibody HD2-4 described in document (1). According to the functional definition of the C face given in the patent in suit which referred only to the ability to agglutinate CRP, these prior art antibodies could thus not be distinguished from those described in claim 1 of the main request and of auxiliary request 1. Since there are contradictions it was proposed to have the experimental reports of

both appellants reproduced by an independent expert, however, document (25) showed that the experimental conditions exerted a considerable influence on the results obtained.

Article 56 EPC
Auxiliary requests 2 and 3

In view of document (5) considered as the closest prior art and disclosing the use of polyclonal antibodies immobilized on latex particles for the determination of CRP, the technical problem to be solved was to improve the accuracy and sensitivity of the CRP determination. The solution defined in claim 1 of auxiliary requests 2 and 3 did not involve an inventive step, because document (5) already pointed at the use of monoclonal antibodies, thus making a link to the monoclonal antibodies described in documents (1) to (4).

This solution was also obvious if document (2), describing the preparation of five monoclonal antibodies used in a turbidimetric assay for the determination of CRP, was considered as an alternative closest prior art, since document (5) pointed at the advantages of monoclonal antibodies in such assays.

The claimed deposited antibodies of auxiliary request 2 were shown in documents (12) and (25) to have the same agglutination behaviour as the antibodies of documents (1) to (4), to which they were no alternatives. The use of the claimed antibodies in a latex agglutination test as defined in the claim of auxiliary request 3 was obvious, since the use of monoclonal antibodies in detection assay or purification procedures was known,

as well as the use of a single monoclonal antibody to agglutinate a multivalent antigen, such as CRP.

X. Appellant I (Patentee) requested that the decision under appeal be set aside and the patent be maintained as granted (main request) or on the basis of the claims of auxiliary requests 1 to 3 all filed during the oral proceedings.

XI. Appellant II (Opponent) requested that the decision under appeal be set aside and that the European patent No. 0 431 171 be revoked.

Reasons for the decision

Article 114(2) EPC

1. Appellant II objected to the late-filing of auxiliary requests 1 to 3 during the oral proceedings. According to the case law of the Boards of appeal of the EPO (4th edition, 2001, pages 545 to 551) relating to the discretion of the boards of appeal under Article 114 (2) EPC if auxiliary requests are "late filed" these may be allowed into the proceedings if they are serious attempts to overcome and to directly answer objections and if they *prima facie* do not provoke new serious formal objections. In the present case, auxiliary requests 1 to 3 were filed to overcome objections raised by appellant II in his statement of grounds of appeal and a later submission.

Furthermore, they are based on the claims as granted or maintained by the opposition division in the following way:

Auxiliary request 1:

Claim 1 is identical to claim 2 as granted, except for the amendment of "*carrying*" into "*performing*". Claims 2 and 6 correspond to claims 3 and 7 as granted in which "*obtainable*" has been replaced by "*obtained*" in response to an objection raised by appellant II during the written appeal procedure. Claims 3 and 5 result from the introduction into claims 4 and 6 as granted of the subject-matter of claim 2 as granted, respectively, whereby in claim 3 "*carrying*" has been amended to read "*performing*". Claim 4 is identical to claim 5 as granted.

Auxiliary request 2:

*C*laim 1 is identical to claim 3 as granted with "*obtainable*" being amended into "*obtained*". Claim 2 results from the combination of the subject-matter of claims 4 and 5 as granted. Claim 3 corresponds to the combination of claims 6 and 7 as granted, in which the word "*obtainable*" has been changed into "*obtained*".

Auxiliary request 3:

The sole claim of auxiliary request 3 is identical to the claim maintained by the opposition division, except for the introduction of a comma separating "*when immobilized on an insoluble carrier*" from "*in a latex agglutination immunoassay*" (cf *supra* section VI).

Therefore, in accordance with the established case law of the Boards of Appeal of the EPO mentioned above, auxiliary requests 1 to 3 are allowed into the proceedings pursuant to Article 114(2) EPC.

Article 123(2)(3) EPC
Auxiliary request 1

2. Objections have been raised under this provision by appellant II. However, there is no need to give detailed reasons whether or not the amendments in the claim are allowable because, as set out below in points 15 to 22, this request has to be rejected for another reason.

Article 54 EPC
Main request

3. The subject-matter of claim 1 of the main request is a monoclonal antibody characterised by its specificity to the **side face** of a disk-like subunit of a C-reactive protein (CRP). The characterising feature "side face" is mentioned in the patent in suit on page 4, lines 18 to 20 ("*In addition, the anti-CRP monoclonal antibodies according to the present invention specifically react with only the side face (C-face) but do not react with the circular upper face (A-face) or the circular lower face (B-face), of a disk-like submit.*" [sic]) and this is illustrated in Figure 1 of the patent in suit which is a schematic drawing showing five disks with an upper and lower face (A and B) separated sharply by a distinct "side face" (C) the disks being arranged in a cyclic pentagonal array.

4. In document (1) CRP also is described as being composed of five identical subunits arranged in a cyclic pentagonal array. The scientific aim of the authors of document (1) was to find monoclonal antibodies recognising epitopes of the CRP molecule. Two monoclonal antibodies are described, EA4-1 and HD2-4, which were shown to bind at opposite sides of the subunits of CRP, these sides being called A- and B-site respectively. No further "site" was identified and in Figures 2 to 5 the authors approximated at what they assumed might be the shape of the subunits by schematically drawing them as egg-like structures. In Figure 5 a model of the CRP molecule is depicted in which the proposed EA4-1 site is slightly medial to the vertical axis of each subunit on the A-face of the molecule. The HD2-4-binding site is depicted on the opposite side of the molecule (B-face) slightly *lateral* to the vertical axis of each CRP subunit. The board agrees with the argument put forward by appellant II that in the absence of clear evidence which model - Figure 1 of the patent in suit or Figure 5 of document (1) - approaches "truth" i.e. the three-dimensional shape of the subunit, it is virtually impossible to draw a reliable line between any "face" of a three-dimensional molecule.

5. Thus, appellant I characterised the antibody of claim 1 of the main request by a feature which is neither described in the patent in suit nor in the prior art in unambiguous technical terms, in order to distinguish the claimed monoclonal antibody from those described already in the prior art. However, a feature supposed to distinguish subject-matter as claimed from the prior

art has to be clear so that it is possible to draw a reliable line between the subject-matter claimed and the prior art, when judging on patentability of subject-matter claimed. However, as it can be concluded from the above, there is no *prima facie* technically reliable disclosure in the patent in suit as to what exactly a CRP subunit's C-face might be.

6. To provide further evidence for the existence of a precise and distinct C-face as depicted in the schematic drawing of Figure 1 of the patent in suit of the subunit of CPR appellant I submitted document (24). Comparative binding experiments with the HD2-4 antibody which is said in document (1) to bind *lateral* on an A-face (see above point 4) and the monoclonal antibodies CRP-1 to CRP-4 as deposited in connection with the patent in suit were carried out and in Figure 8 of document (24) again a schematic drawing of the five subunits of CRP is depicted with the putative recognition sites of these antibodies. The board observes that here the subunits are depicted as egg-like structures. Further and above it seems difficult to clearly distinguish the recognition sites for HD2-4 (a prior art antibody) and for example CRP-3 (one of the antibodies of the patent in suit). Document (24) further shows a computer model - extrapolated from an electron micrograph also shown therein - which is said to show the binding of the deposited monoclonal antibodies with their Fab arms at the "edges" (C-faces) of the subunits of CRP. The board accepts that the computer model might be interpreted this way but agrees with appellant's II position that there is no evidence on file of a convincing technically causal connection between the electron micrograph and the computer model.

7. Technical evidence for a "site" different from the A- and B-site as already postulated in document (1) was submitted by appellant I with document (24) in order to support the data provided in Example 4 of the patent in suit, an experiment in which the A- and B-site were masked by respective antibodies, so that positive binding data for a further antibody could have been seen as further supporting the data given in the patent in suit and insofar possibly indicative for a "site" different from the A- and B-site. However, in the experiments in document (24) only B-site specific antibody HD2-4 was used to mask a CRP subunit so that one cannot draw a reliable conclusion on exactly where the antibodies CRP-1 to CRP-4 of the patent in suit bind.

8. Appellant I argued in the statement of grounds of appeal (page 7, last paragraph) that, since document (1) mentions the existence of upper and lower faces in the CRP molecule, there must also be a side face. Confirmation thereof was seen in the sentences in document (1) on page 2412 (left column) referring to the *planar surfaces* of the CRP molecule. The term "*planar surfaces*" is used on page 2412 of document (1) with reference to Figures 2A and 2B showing HD2-4/CRP complexes, in which B-face specific antibody HD2-4 is said to protrude from only one of the *planar surfaces* of the CRP molecule, thus identifying one of these planar surfaces as the B-face. The second planar surface is shown in Figure 3 as the A-face on which antibody EA4-1 binds. However, the board sees this as a reference to the A- and B-faces and is unable to draw from this the firm conclusion to a C-face in the

absence of reliable technical evidence about the three-dimensional shape of a CRP subunit. The binding data as such may be accepted as indicative for a binding taking place at a different epitope but not as reliable evidence that these epitopes are representative for a side face being different from those described already in the prior art, i.e. A- and B-face. Finally, it is to be noted that the term "planar surfaces" is used in document (1) in relation to the whole pentameric CRP molecule and not to the CRP subunit as characterised in claim 1.

9. Appellant I further argued in support of a clear definition of a C-face that the steric hindrance caused by the huge size of the latex particles to which antibodies are bound in comparison to that of the CRP molecule and of the antibodies would preclude an agglutination reaction by an antibody other than a C-face specific one, as shown in document (7), a schematic representation at scale of the interaction between latex bound antibody and CRP in an agglutination reaction. Appellant II has, however, in the board's view, put into question this argument by submitting document (17), which is a modification of document (7) and shows that agglutination can well be obtained with latex bound antibodies reacting with the A- or B-faces of the CRP molecule.

10. Appellant I further argued for an existence of a side- or C-face in the CRP molecule on the basis of agglutination experiments described in Example 4 of the patent in suit and in *Experiment 3-2* of document (24), which concerns an analysis of the interaction of the CRP-1 to CRP-4 antibodies described in the patent in

suit and of a prior art B-face specific antibody (HD2-4) with the CRP molecule. These results have been schematically presented in document (27), which was submitted in response to a question raised by the Board in its communication because in document (24) only a B-face specific antibody was used and not, as in Example 4 of the patent in suit both A- and B-face specific ones. In *Experiment 3-2* of document (24), CRP-1 bound to a microtiter plate is reacted with CRP, the B-face of which is masked by B-face specific antibody HD2-4. Biotinylated CRP-1 is then added as well as the avidine-peroxydase detection system. Document (27) shows in its right part that, assumed CRP-1 bound to the CRP A-face, then the CRP molecule was placed parallel to the microtiter plate with the A-face turned to the microtiter plate and there was a steric hindrance preventing biotinylated CRP-1 and the avidine-peroxydase detection system from binding to the A-face, with the consequence that there should not be a reaction. Since, however, a reaction does occur (document (24), Figure 4), it has to be concluded (document (24), last page) that the binding of CRP-1 must necessarily occur on a further, i.e. C-face, as explained in the left part of the schematic representation of document (27).

11. However, this conclusion was answered by appellant II in that neither the CRP molecule, nor the antibody CRP-1 are of the rigid structure which would explain steric hindrance. Antibodies are known, because of their structure, to be flexible molecules. Furthermore, the conclusion of document (27) is in contradiction with the teaching of document (1) in which the reaction of CRP with B-face specific antibody HD2-4 is said on

page 2412 (left column, last paragraph and right column, first paragraph) to also result in flattened complexes such as those depicted in Figure 2A and 2F. It is technically plausible that such flattened complexes with immobilized CRP-1 binding on the A- or B -face of CRP, would cause no steric hindrance and would allow the binding of biotinylated CRP-1 and the avidine-peroxydase complex on the CRP A- or B-face.

12. From the above it follows that appellant I could not convince the board, that the feature used to distinguish his invention from the prior art - here the feature of the monoclonal antibody of claim 1 under consideration to react specifically with the side face of a disk-like subunit of CRP - is precisely and reliably described in the patent in suit or in the supporting documents (24) and (27). This feature is thus vague and open to interpretation when it comes to a judgement on whether or not an antibody of the prior art falls under this term.

13. In document (1) (see above points 7 and 8) the antibody HD2-4 is said to bind to a place at the CRP which is called B-face. Whilst the board would accept from the data given in Example 4 of the patent in suit where the B-face was "masked" by an B-face-antibody, that antibody HD2-4 may bind at a different epitope of a CRP subunit than the antibodies of the patent in suit exemplified by deposits of the respective hybridomas producing them the board is unable to safely conclude that the epitope at which these antibodies bind is situated at a place on the subunit defined as C-face, as claimed.

14. It follows that the antibodies described in documents (1) to (4) are encompassed by the subject-matter as defined in claim 1 of this request which is, therefore, not novel and does consequently not fulfil the requirement of Article 54 EPC and the request has to be rejected.

Auxiliary request 1

15. The antibody of claim 1 of auxiliary request 1 is, in addition to the above considered feature, further characterised by its capability to agglutinating CRP, this agglutination being said to result from an interaction with the CRP C-side (or C-face) when immobilized on an insoluble carrier. Contrary to the feature C-side (or C-face) the further feature to agglutinating CRP is a well established technical characterisation which is not contested by appellant II. It is mentioned in Example 4 of the patent in suit.

16. It is appellant's II position that the feature to agglutinate cannot distinguish the subject-matter of claim 1 of this request from monoclonal antibodies described in the prior art. To support this appellant II filed experimental reports (documents (10) to (12)) in which antibodies CRB017 and CRB018 as described in documents (2) to (4) are shown to cause an agglutination reaction with CRP. In particular document (11) shows that antibody HD2-4 of document (1) and antibodies CRB017 to CRB020 and CRB023 of documents (2) to (4) agglutinate CRP, when immobilized on latex particles. The experiments of documents (10) and (11) are further confirmed in document (12), another experimental report on the CRP agglutination ability of

prior art antibodies HD2-4 and CRB017 and CRB018. Finally, the CRP agglutination ability of the prior art antibodies is again shown in document (25), an experimental report submitted in response to the experiments carried out by appellant I in document (24). Document (25) also shows experiments concerning the competitive inhibition of the CRP agglutination of the antibodies of the patent in suit by the antibodies of documents (2) to (4).

17. In document (6), however, a declaration under Rule 132 before USPTO by one of the inventors, the antibodies of the patent in suit are shown to agglutinate CRP but not those of documents (2) to (4).

18. The results of all these experiments carried out by appellants I and II in order to provide evidence for their respective cases are, thus, *prima facie* contradictory. In the following the board will evaluate the evidence on file including the disclosure in the prior art documents.

19. The experiments by appellant II were carried out to confirm the disclosure of documents (2) to (4) where, in particular in document (4) in Figure 3, there is shown that precipitin lines are formed by the monoclonal antibodies and CRP, a reaction which is normally not observed with monoclonal antibodies but rather with polyclonal antibodies. This is emphasised in particular in document (3), page 20, lines 17 to 23, dealing with the same monoclonal antibodies as document (4), where this capability of the respective monoclonal antibodies is appreciated by the words: *"A very wide range of applications is expected with these antibodies*

which were produced, since they allowed the same level of precipitation reaction as polyclonal antibodies, though being monoclonal antibodies for which precipitation reaction is currently difficult to achieve, ...". The board remarks that, whilst the expression "agglutinating" is used in the claim under consideration which represents the narrow term for an antigen/antibody interaction, documents (3) and (4) speak about "precipitation" which has a broader meaning. In the given context of a reaction between antigens (CRP subunits) and antibodies, however, these terms mean the same molecular phenomenon. The experiments carried out by appellant II in documents (10) to (12) thus confirm the disclosure of the prior art.

20. Whilst the board is prepared to accept that appellant I carried out their experiments with care in order to show that the prior art monoclonal antibodies do not agglutinate, it seems that experimental conditions like concentration of the antibody-peroxydase complex and incubation time with the colour reagent as shown in point 1 (page 3, lower part to end of page 4) of document (25) influence the results of the agglutination reaction. This is further exemplified by the comparison of "*Versuch 1*" and "*Versuch 1.1*" on diagrams 1 to 6. Thus, the contradiction between the results provided by the parties can well be explained by applying different experimental conditions.

21. The board notes that claim 1 does not specify the conditions under which the agglutination reaction takes place. This means that antibodies which only under certain conditions agglutinate are also embraced by the subject-matter of the claim. The experiments carried

out by appellant II show that under the chosen conditions the antibodies described in documents (2) to (4) do agglutinate. The board has no reasons to doubt that also these experiments had been carried out with care. Furthermore appellant I did not provide evidence that under the conditions selected by appellant II agglutination does not take place.

22. In view of the foregoing, the experiments submitted by appellant I and supposed to counter the precipitation data given in documents (2) to (4) for the monoclonal antibodies isolated there and the experiments filed by appellant II in documents (10) to (12) and (25) cannot assist his case. Since, therefore, there are monoclonal antibodies described in the prior art which agglutinate CRP under certain conditions, this feature cannot distinguish the subject-matter of claim 1 of auxiliary request 1 from the antibodies disclosed in the prior art documents (2) to (4), so that the subject-matter of claim 1 does not fulfil the requirement of Article 54 EPC. Therefore, auxiliary request 1 has to be rejected.

Auxiliary request 2 and 3
Articles 83, 123(2)(3) and 54 EPC

23. No objections have been raised by appellant II against claim 1 of auxiliary requests 2 and 3 in view of these Articles and the Board also sees none.

Auxiliary request 2
Article 56 EPC

24. Claim 1 of auxiliary request 2 is directed to the four deposited antibodies CRP-1 to CRP-4 obtained by their

respective hybridomas. The Board shares the view of appellants I and II in considering document (2) as the closest prior art. It describes the preparation of monoclonal antibodies CRB17 to CRB20 and CRB23 which are further used in a determination assay for CRP. Document (2) also mentions the use of latex-antibody particles as a prior art method for the determination of an antigenic substance against which the antibodies have been raised.

25. The technical problem to be solved in view of document (2) can then be defined as the provision of alternative monoclonal antibodies for the determination of CRP.

26. In 1989, the priority year of the patent in suit which is thirteen years after the technology to produce monoclonal antibodies had been developed, the preparation of monoclonal antibodies was a matter of routine experiment. Therefore, no inventive merit can be seen in the method as such to provide the monoclonal antibodies. Further, the search as such for monoclonal antibodies, given that the problem to be solved is an alternative, is not inventive either because there is an incentive in this art to look for useful antibodies. In document (12) antibodies CRB17 and CRB18 of documents (2) to (4) are further shown (Table on page 2) to have an affinity for CRP identical or at least very similar to that exhibited by the antibodies of the patent in suit. The particular and deposited antibodies which are the subject-matter of claim 1 of auxiliary request 2 thus do not provide the art with any unexpected property or functional advantage in the sensitivity or the specificity, for instance, and are not functionally different from those described in

document (2). The case law in this field acknowledges inventive step if and when there is evidence that a claimed monoclonal antibody prepared by routine methods shows unexpected properties (cf decision T 645/02 of 16 July 2003). If, however, there are no unexpected effects achieved with a further monoclonal antibody compared with a monoclonal antibody with essentially the same properties as desired the case law denies inventive step (cf decision T 512/94 of 23 June 1998).

Thus, claim 1 of auxiliary request 2 does not fulfil the requirement of Article 56 EPC and this request has also to be rejected.

Auxiliary request 3
Article 56 EPC

27. The sole claim of auxiliary request 3 is also directed to the four deposited monoclonal antibodies, but differs from claim 1 of auxiliary request 2, in that it is formulated as a use-claim wherein a single antibody is used in a latex agglutination assay. This definition aims at pointing to the capability of the claimed antibodies to agglutinate, a feature which is known to not normally be connected to monoclonal antibodies but rather to polyclonal antibodies (see also point 19 above). In view of this, the Board agrees with appellants I and II in considering document (5) as the closest prior art. This document describes the preparation of polyclonal anti-CRP antiserum-latex particles (Example 3) and their use for the determination of CRP concentration in serum probes (Example 4) by nephelometry following an agglutination reaction (page 6, lines 1 to 3).

28. The technical problem to be solved in view of the teaching of document (5) can be defined as to improve the sensitivity of the determination.

29. Document (5) already points at the use of monoclonal antibodies which are said on page 6 (lines 29 and 30) to be advantageous in the preparation of such latex complexes. Whilst the board would accept that such a general indication to switch from polyclonal antibodies to monoclonal antibodies - once the technology to produce them via the hybridoma was routine and the advantages of identity and high amount production of these monoclonal antibodies are obvious - might not necessarily be against the acknowledgement of an inventive step, there is in particular cases the inherent disadvantage of monoclonal antibodies that they do not agglutinate when used singly. However, the monoclonal antibodies described in documents (2) to (4), as shown above in points 15 to 22, do agglutinate and thus are already ones which show characteristics not normally expected with monoclonal antibodies. The skilled person was, therefore, by the disclosure of documents (2) to (4), provided with the teaching that monoclonal antibodies against CRP existed which solved already the above stated problem so that the provision of further antibodies with this feature is not inventive. The board further observes that CRP was known at the priority date of the patent in suit to be a pentameric molecule (document (1), page 2411, left column, last paragraph) with five identical subunits. The skilled person could *prima facie* derive from this that each subunit of the CRP molecule carries the same epitopes with the consequence that each epitope is

present five times on the CRP molecule. This makes it a multivalent molecule and hence suited for an agglutination reaction with a single monoclonal antibody. Therefore, the use of a single antibody in the agglutination reaction cannot be considered as a feature suitable to contribute to the inventive step of the subject-matter of the claim.

30. It follows from the foregoing that the subject-matter of claim 1 of auxiliary request 3 does not involve an inventive step in view of the teaching of document (5) combined with any one of documents (2) to (4) and does not fulfil the requirement of Article 56 EPC. Also this request has to be rejected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey